IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Endre Markovits Schersl	§	
		§	Art Unit: 1617
Serial No.:	09/922,532	§	
		§	Examiner: B. P. Badio
Filed:	August 3, 2001	§	
		§	
Title:	Pharmaceutical and food compositions containing "wood alcohols" or " wood sterols" useful for lowering serum cholesterol	§	

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Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

APPEAL BRIEF PURSUANT TO 37 C.F.R. §1.191

Appellants take this appeal from the October 25, 2007, Final Office Action in the above-identified application. A Notice of Appeal was filed on February 7, 2008.

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1. REAL PARTY IN INTEREST

The real party in interest is Harting, S.A., having a place of business at Americo Vespucio 2680, Conchali, Santiago, Chile.

2. RELATED APPEALS AND INTERFERENCES

Appellants know of no other appeal or interference that will directly affect, or be directly affected by, or that will have a bearing on the Board's decision in the pending appeal.

3. STATUS OF CLAIMS

Claims 57 and 59-63 are rejected. Claims 57 and 59-63 are the claims on appeal. A copy of the pending claims is attached as Appendix A.

4. STATUS OF AMENDMENTS

There are no amendments pending.

5. SUMMARY OF CLAIMED SUBJECT MATTER

One aspect of the invention relates to a method for lowering serum level of cholesterol comprising the step of orally administering a composition comprising a mixture of policosanols, said mixture consisting essentially of from about 1 % to about 5 % by weight of 1-eicosanol, from about 5 % to about 30 % by weight of 1-docosanol, from about 20 % to about 60 % by weight of 1-tetracosanol and from about 15 % to about 50 % by weight of 1-hexacosanol. See claim 1 and Specification, page 3, Table I.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

(a) **Claims 57 and 59-63 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Fuenzalida et al.* (European Patent Specification 952,208), *Sorkin, Jr.* (U.S. Patent 5,952,393), *Gamble et al.* (U.S. Patent 6,596,776), *Cleary* (U.S. Patent 4,495,094), *Milstein et al.* (U.S. Patent 6,394,230) and *Jones et al.* (Metabolism, 1998) in combination.**

7. **ARGUMENT**

(a) Claims 57 and 59-63 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Fuenzalida et al. (European Patent Specification 952,208), Sorkin, Jr. (U.S. Patent 5,952,393), Gamble et al. (U.S. Patent 6,596,776), Cleary (U.S. Patent 4,495,094), Milstein et al. (U.S. Patent 6,394,230) and Jones et al. (Metabolism, 1998) in combination.

An invention that would have been obvious to a person of ordinary skill at the time of the invention is not patentable. *See* 35 U.S.C. 103(a). As reiterated by the Supreme Court in *KSR International Co. v. Teleflex Inc. (KSR),* 550 U.S. ___, 82 USPQ2d 1385 (2007), the framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows: (A) determining the scope and content of the prior art; (B) ascertaining the differences between the claimed invention and the prior art; and (C) resolving the level of ordinary skill in the pertinent art.

The Examiner's assertions regarding the prior art.

Appellants' claims pending on appeal are for a novel method for lowering serum level of cholesterol comprising the step of orally administering a composition comprising a mixture of policosanols, said mixture consisting essentially of from about 1 % to about 5 % by weight of 1-eicosanol, from about 5 % to about 30 % by weight of 1-docosanol, from about 20 % to about 60 % by weight of 1-tetracosanol and from about 15 % to about 50 % by weight of 1-hexacosanol.

From the Office Action dated November 29, 2006,

> "Each of Fuenzalida, Sorkin, and Gamble teaches policosanols, i.e., long chained aliphatic alcohols are useful in lowering plasma cholesterol levels.
> Fuenzalida teaches the presence of fatty alcohols such as eicosanol, docosanol, tetracosanol and hexacosanol in tall oil and Cleary teaches the presence of octadecanol in tall oil.
> Each of Gamble, Milstein and Jones teaches the incorporation of the cholesterol-lowering agents, such as mixtures, of aliphatic alcohols, into food substances such as margarine is known in the art.
> Based on the prior art as discussed above, the utilization of a composition comprising long chained aliphatic alcohols in lowering

plasma cholesterol levels would have been obvious to the skilled artisan in the art at the time of the present invention.
The instant claims differ from the cited prior art by reciting specific ranges of eicosanol, docosanol, tetracosanol, and hexacosanol with or without a specific amount of octadecanol. However, determination of the amounts of each alcohols in the composition that would be effective in lowering cholesterol level requires only routine experimentation which was within the level of skill of the ordinary artisan in the art at the time of the present invention. Therefore, the specific ranges of the active ingredients is not patentable absence a showing of criticality which is not present in the present specification."

Ascertaining the differences between the claimed invention and the prior art

The present invention claims a policosanol whose composition is strikingly different, differing in orders of magnitude, in many respects from the policosanols disclosed in the cited references. Applicant contends that each of the cited references, both singularly and in combination, do not teach, suggest, or anticipate the present composition and that effective amounts of policosanols. (See Table 1 below).

TABLE I:

RANGE OF COMPOSITIONS IN WEIGHT % OF POLICOSANOLS FROM DIFFERENT SOURCES

Alypathic Alcohols Name (Number) of carbon atoms in molecule	**EP 952 208 (Fuenzalida)**	**US Pat. No. 5,952,393 (Sorkin) Rice Bran Wax**	**US Pat. No. 6,596,776 (Gamble) Beeswax**	**Claim 57**
Octadecanol (18)	0	0	0	1-10
Eicosanol (20)	3.3-3.6	0	0-5	5-25
Docosanol (22)	4.0-4.4	1-1.6	0-5	20-60
Tetracosanol (24)	2.5-3.1	9.7-14	12-30	20-50
Hexacosanol (26)	0.2	8.9-12.7	13-30	1-5
Heptacosanol (27)		0	0-5	0
Octacosanol (28)		16.9-24.3	12-25	0
Nonacosanol (29)		0	0	0
Triacontanol (30)		25.3-36.3	20-40	0
Dotriacontanol (32)		14.1-20.2	5-15	0
Tetratriacontanol (34)		6.7-9.6	0-5	0
Hexatriacontanol (36)		1.5-2.2	0	0

Fuenzalida teaches the presence of fatty alcohols such as eicosanol, docosanol, tetracosanol and hexacosanol in tall oil. Regarding cholesterol lowering diets, Fuenzalida teaches that reduced forms of sterols, known as stanols, are used. Sterols or stanols and policosanols constitute different classes of chemical compounds. The policosanol compositions

of Sorkin and Gamble, known for cholesterol lowering activity, contain ***eight or nine*** different policosanols with carbon numbers ranging form 18 to 36.

The Examiner states: "The art teaches policosanols, alone or in combination, and their ability to lower plasma cholesterol levels. The claimed invention is a combination of previously known elements in a predictable art area." However, the art actually teaches **certain policosanol mixtures** are useful in lowering plasma cholesterol. These mixtures are those shown in the table above. Combination of the prior art policosanol mixtures, however, does not arrive at the claimed invention, four policosanol constituents with a narrow range of carbon numbers, C18-C26. All of the references are combinations of eight or nine policosanol constituents over a large range of carbon numbers (C20-C36). The policosanol mixtures of Sorkin and Gamble cannot be combined to form the policosanol mixture of the claimed invention. Even if you were to combine the references to include Fuenzalida, the claimed policosanol mixture is not obtained. The Applicant has taken the genus of policosanols (constituents of plant and insect waxes) which were known to possess cholesterol lowering effects and produced a species (from tall oil) of the genus not previously known to possess such cholesterol lowering effects. The lower carbon alcohols were not known to have cholesterol lowering effects. Even if tall oil policosanols were thought to have cholesterol lowering effects, the Applicant refined the composition to only include four components of the lower end carbon number alcohols.

Resolving the level of ordinary skill in the pertinent art

In contrast to the Examiner's assumption, one of ordinary skill in the art would not assume that "all" plant alcohols, no matter the carbon number would have cholesterol lowering effects. The prior art shows that alcohols with higher carbon numbers would have cholesterol lowering effects. However, given the inherent unpredictability of the chemical arts, particularly in combination with the unpredictability of the physiological effects of chemicals, negates the Examiner's assumption. *See, e.g., Takeda Chem. Indus., Ltd. v. Alphapharm PTY., Ltd.*, 492 F.3d 1350, 1361, 83 USPQ2d 1169 (Fed. Cir. 2007) (cautioning against generalization that specific chemical structures are prima facie obvious one to the other). That is, there is substantial uncertainty on the effect of even small changes in the constituents of a policosanol mixtures on a mixture's hypocholesterolemic activity. Thus, it may be obvious to the person of ordinary skill to prepare novel mixtures by combining the known and effective mixtures. In contrast, however, a skilled artisan would not have been led to formulate the claimed mixtures

which include policosanols different from those disclosed by the prior art. Moreover, the selection of the specific four policosanols of the claimed invention, in the amounts claimed, would not have resulted from routine experimentation with prior art mixtures containing eight or more components.

In fact, applicants respectfully point out that the art clearly shows that policosanols from different natural sources are not readily interchangeable, nor do they exhibit the same therapeutic effects. In fact the art shows that policosanols from different origins exhibit different therapeutic effects, including specifically different hipocholesterolemic effects. For example, U.S. Patent No. 6,465,526 discloses bee wax and sugar cane policosanols, which were tested in several pharmacological applications. In one such test, the hypocholesterolaemic activity of these policosanols was investigated. Example 11 of the '526 patent discusses these tests, as follows:

EXAMPLE 11

> Is done a comparative study between the properties of the natural mixtures of higher primary aliphatic alcohols obtained from bee wax (M.H.A.A.B.W.), object of the present invention, and that of the higher primary aliphatic alcohols obtained from sugar cane wax (EPC 0 488 928) (named M.H.A.A.S.C.W. since this moment). This study permit the possibility of establishing that both mixtures not only differs in the number of alcohols and in the relative composition of the alcohols present in both of them, but also, in its pharmacological profile, in different experimental models traditionally used in the pharmacological screening, are also different. For that reason are developed the experiments that are described as follows:
> a) anti-inflamatory effect: In order to corroborate the anti-inflamatory effect of both mixtures, the models of pleuresy by carragenine and granule by cotton were used, doses of 100 and 200 mg/kg, respectively, were used.
> b) antiulcer effect: In order to corroborate the antiulcer effect of both mixtures it was used the experimental methodology previously described in Example 8 of the present invention, using doses of 25 mg/kg of corporal weight for both mixtures.
> c) hipolipidemic effect: Male New Zealand rabbits were used and divided in the following groups a) controls, b) M.H.A.A.B.W. (5 mg/kg) and c) M.H.A.A.S.C.W. (5 mg/kg) administered orally during 1 month. Each 15 days blood samples were taken in order to determine the lipidic parameters (total cholesterol, triglycerides, HDL-C, LDL-C and VLDL-C).
> d) antiischemic effect: For the analysis of both mixtures over the cerebral ischemia it was used the model in which cerebral ischemia is provoked in Mongolian gerbils by carotide ligature. Female Mongolian

gerbils, of 60 to 80 g of weight, were used that were adapted to laboratory conditions for free access to food and water. Both mixtures were administered by i.p. route using for this purposes a suspension in a 2% Tween 20/water vehicle. The animals were distributed in the following experimental groups: 1) control (vehicle 2% Tween 20/water), 2) M.H.A.A.B.W. (200 mg/kg) and 3) M.H.A.A.S.C.W. (200 mg/kg).

The ligature of the left common carotide was done anaesthetizing the animals with an ether atmosphere. The animals were observed for 24 h, registering the appearance of clinical symptoms of cerebral damage, such as circling, rolling and convulsions, as well as the number of deaths produced during the experiment.

e) antiplatelet aggregation effect: In order to corroborate the effect of both mixtures on the platelet aggregation in rats, induced by ADP or collagen, a number of male Sprague Dawley rats, weighing 250-350 g, were used. Each one of the mixtures was administered orally as a suspension in an acacia gum/water vehicle (1 mL/100 g body weight) for 4 weeks using gastric gavage. The animals were randomly distributed in 3 experimental groupsa) control (only received vehicle), b) M.H.A.A.B.W. (25 mg/kg) and c) M.H.A.A.S.C.W. (25 mg/kg).

For the development of the platelet aggregation assay, the rats were anaesthetized in ether atmosphere. After the abdomen is open, blood was extracted (5 mL) from cava vein and mixed with 3.8% sodium citrate (1 volume of sodium citrate for 9 volumes of blood). The platelet rich plasma (PRP) was obtained by blood centifugation and the platelet poor plasma (PPP) was obtained by centrifugation of PRP aliquots at 330 g for 15 min. Platelet aggregation was induced by ADP or collagen and was registered in a Payton aggregometer.

f) antithrombotic effect: For the study of the antithrombotic effect the venous thrombosis model was used. The following treatments were administered for these purposes: 1) control, 2, 3, 4) M.H.A.A.B.W. (25, 50 and 100 mg/kg), respectively and 5, 6, 7) M.H.A.A.S.C.W. 25, 50 and 100 mg/kg) respectively.

Rats were anaesthetized with sodium phentobarbital (40 mg/kg) by i.p. route. Later on, were injected with hipotonic saline solution (0.22% NaCl) (1 mL/100 g body weight) by the femoral vein. A minute later, the abdomen was opened and the cava vein was exposed, isolated and ligatured passing a thread through the vein. The abdomen was closed, provisionally, for 10 min, later on, it was reopened and the cava vein was ligatured again, 2 cm below the first ligature. Immediately, it was removed and longitudinally opened, the thrombo was removed and was set in a humid oven at room temperature, being weighed 1 hour later.

The results obtained after the development of all these pharmacological assays are summarized in Table 17.

TABLE 17

Comparative effect between the natural mixture of alcohols obtained from bee wax and those obtained from sugar cane wax

Assay	M.H.A.A.S.C.W.	M.H.A.A.B.W.
Anti-inflamatory	+	-
hipolipidemic effect	-	+++
antiischemic	+	+++
antiulcer	+++	+
antiplatetlet aggregation	-	+
antithrombotic	-	+

with activity:
(+) discrete
(++) moderated
(+++) higher
(-) without any activity

As can be observed, from these results, the pharmacological properties of both natural mixtures of higher primary aliphatic alcohols are differents, only in the antiulcer effect both mixtures exhibit activity, but, as can be shown in the Table, the effect of the mixture of alcohols obtained from bee wax (M.H.A.A.B.W.) is much more effective than that obtained from sugar cane wax (M.H.A.A.S.C.W.).
'526 patent, col. 12, line 29 – col. 14, line 5.

The art further shows that policosanols from specific, natural origins have different therapeutic, including hypocholesterolaemic, activity than synthetic higher alcohols, such as pure hexacosanol and pure octacosanol. Specifically, U.S. Patent No. 5,663,156 discloses that pure hexacosanol and pure octacosanol have no statistically significant cholesterol-lowering effect, as follows:

EXAMPLE 11

Male New Zealand rabbits were distributed randomly in 4 groups: a control group (only receiving vehicle by gastric gavage) and 3 groups treated M.H.P.A.A., octacosanol and hexacosanol, respectively at 5 mg/kg. Serum lipid profile was determined at baseline and 30 days before treatment. M.H.P.A.A. decreased significantly total cholesterol and LDL-C. Moreover, levels of cholesterol, LDL-C and triglycerides of M.H.P.A.A.-treated rabbits were significantly lower than those of the controls. Nevertheless, the changes on serum lipid profile occurred in groups treated with octacosanol or hexacosanol did not achieve statistical significance as is shown in Table 13.

TABLE 13
Effects of M.H.P.A.A., octaconsanol and hexacosanol on serum lipid profile (mmol/L) of New Zealand normocholesterolemic rabbits (mean values)

Group	Dose (mg/kg)	Baseline	After treatment
Total cholesterol			
Controls	0	2.5	2.3
M.H.P.A.A.	5	2.8	1.6 *+
Octacosanol	5	2.7	2.2
Hexacosanol	5	2.6	2.4
LDL-C			
Control	0	1.5	1.2
M.H.P.A.A.	5	1.3	0.6 *+
Octacosanol	5	1.4	0.9
Hexacosanol	5	1.5	1.0
Triglycerides			
Control	0	0.80	0.82
M.H.P.A.A.	5	0.78	0.55 *
Octacosanol	5	0.77	0.70
Hexacosanol	5	0.80	0.78

* $p < 0.05$ comparison with controls (Mann Whitney U test)
+ $p < 0.05$ comparison with baseline (Wilcoxon)
'156 patent, col. 12, line 49 – col. 13, line 22.

Thus, the art clearly demonstrates that the policosanol composition profile and source are critical in determining hypocholesterolaemic activity. Thus, it would not have been obvious to one of ordinary skill in the art to use policosanols and phytosterols and mixtures thereof derived from tall oil to achieve hipocholesterolemic benefits.

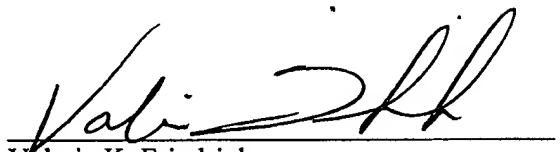
In addition, the Examiner has not cited a reference which shows a single policosanol, not in a mixture, having a cholesterol lowering effect. By contrast, the Applicants have called attention to the Gamble reference (U.S. Patent 6,465,526, Example 11) wherein neither octacosanol nor hexacosanol, the main constituents of sugarcane wax policosanols show cholesterol lowering effects, reflecting the highly unpredictable nature of the art. Therefore, it would not have been obvious to a skilled artisan to reduce the number of components by half, or less, to achieve a combination of policosanols having a cholesterol lowering effect, much less improved cholesterol lowering effect. The references the Examiner has found are for combinations of policosanols, having numerous components over a wide range of carbon

numbers. There is no predictability in the art to say that mixtures of policosanols having only a few lower carbon number components would be as effective as the art has shown. Applicant found a species of the genus which previously had not been known to have the same cholesterol lowering effects.

Dependent claims 59-63 depend from claim 57 and are therefore allowable for at least the same reasons as discussed above. If an independent claim is nonobvious under 35 U.S.C.§103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Accordingly, the rejection of these claims should be reversed.

The Commissioner is hereby authorized to charge Deposit Account No. 50-3420, reference 22106965-105181(VKF) for the fee of $255.00 required by 37 C.F.R. § 41.20(b)(2) and any additional fees inadvertently omitted which may be necessary.

Respectfully submitted,



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Appendix A: Clean Copy of Current Pending Claims

1 – 56. (cancelled)

57. (Previously Presented) A method for lowering serum level of cholesterol comprising the step of orally administering a composition comprising a mixture of policosanols, said mixture consisting essentially of from about 1 % to about 5 % by weight of 1-eicosanol, from about 5 % to about 30 % by weight of 1-docosanol, from about 20 % to about 60 % by weight of 1-tetracosanol and from about 15 % to about 50 % by weight of 1-hexacosanol.

58. (Previously Presented)

59. (Previously Presented) The method of claim 57 further comprises one or more pharmaceutically acceptable carrier components.

60. (Previously Presented) The method of claim 59 wherein the pharmaceutically acceptable carrier components are selected from the group of binders, lubricants, stabilizers, preservatives, diluents or coating agents.

61. (Previously Presented) The method of claim 57 wherein the composition further comprises adding the composition to a food substance selected from the group consisting of edible oil, margarine, butter, salad dressing, milk and beverages.

62. (Previously Presented) The method of claim 57 further comprises one or more pharmaceutically acceptable carrier components.

63. (Previously Presented) The method of claim 62 wherein the pharmaceutically acceptable carrier components are selected from the group of binders, lubricants, stabilizers, preservatives, diluents or coating agents.

Appendix B: Evidence

Not applicable.

Appendix C: Related Proceedings

Not applicable.